Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology

Date:	July 6, 2010
To:	Thomas Laughren, M.D., Director Division of Psychiatry Products (DPP) Office of New Drugs (OND)
Through:	Mark I. Avigan, M.D., C.M., Director Division of Pharmacovigilance (DPV) I
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Subject:	Death with the concomitant use of clonidine or guanfacine and amphetamine/dextroamphetamine or dexmethylphenidate or dextroamphetamine or lisdexamfetamine or methylphenidate
Drug Name(s):	Clonidine, guanfacine, amphetamine/dextroamphetamine, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, methylphenidate
Application Type/Number:	See Appendix A
Applicant/sponsor:	See Appendix A
OSE RCM #:	2010-1046

CONTENTS

EXECUTIVE SUMMARY

The purpose of this review is to determine whether the current labels for methylphenidate and dexmethylphenidate products, which have a drug interaction statement cautioning clinicians about serious adverse events that may occur with concomitant use of methylphenidate (a psychostimulant) and clonidine (an alpha$_2$ adrenergic agonist), require updating. This drug interaction caution first appeared in labeling in 2000 with the approval of Concerta. The statement was apparently based upon four case reports of seriously life-threatening adverse reactions or death with the combination of stimulants and clonidine, despite the fact that these cases were reviewed by DPP at the time with a conclusion that there was no clear relationship between death and the combination of methylphenidate and clonidine. Nonetheless, the cautionary statement about a potential drug-drug interaction appeared in the Concerta label in 2000 and after that appeared in the other methylphenidate labels without an apparent critical review of cases.

This issue has public health importance because stimulants and clonidine are often used in standard-of-care psychiatry practice to treat attention deficit hyperactivity disorder (ADHD). This has been an off-label clinical practice for many years, but recently DPP has had applications for the use of alpha$_2$-adrenergic agonists for the monotherapy and adjunctive (to stimulants) treatment of ADHD. DPP currently asks sponsors of selective alpha$_2$-adrenergic agonists that they be studied as adjuncts to stimulants in new drug applications seeking the indication of the treatment of ADHD, because it is common clinical practice to use members of these two drug classes together.

Therefore, the Division of Psychiatry Products (DPP) requested that the Division of Pharmacovigilance I (DPV I) search the Adverse Event Reporting System (AERS) database for cases of death associated with the concomitant use of selective alpha$_2$ adrenergic agonists (clonidine or guanfacine) and stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts).

In addition to the AERS search, DPP has evaluated controlled clinical trial data from applications for the alpha$_2$-adrenergic agonists submitted for the indication of adjunctive (to stimulants) treatment of ADHD.

This joint effort identified only one new case of death in the AERS database, which reported the concomitant use of clonidine and methylphenidate, and no cases of serious and unexpected adverse events from the clinical trials data

Based on the data reviewed, in the absence of published or other data that points to risk for adverse events, we recommend updating the current methylphenidate and dexmethylphenidate labels to remove the drug interaction statement regarding methylphenidate and clonidine..

1 INTRODUCTION

The purpose of this review is to determine whether the current labels for the methylphenidate and dexmethylphenidate products, which have a drug interaction statement warning clinicians about serious adverse events that may occur with concomitant use of methylphenidate and clonidine, require updating. DPP requested that DPV I search the AERS database for cases of death associated with the concomitant use of alpha agonists (clonidine or guanfacine) and stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts). Additionally, DPP requested that we specifically focus on cases of death that did not report co-existing physical disorders known or suspected to be associated with death, or

deaths with known causes unrelated to an underlying medical condition (e.g. accidental deaths, homicides, motor vehicle accident, natural disease progression, overdoses, or suicides).

1.1 BACKGROUND

In 2000, Concerta® (methylphenidate hydrochloride) received FDA approval; this approval marked the first time that a methylphenidate label included a statement regarding a potential drug interaction between methylphenidate and clonidine. This potential drug interaction was first reported in 1995 in a broadcast from National Public Radio, followed by an article in the literature that described four reports from the FDA AERS database of life-threatening or fatal cases associated with the concomitant use of methylphenidate and clonidine.[1] The author concluded that the cases were not convincing of a drug interaction between clonidine and methylphenidate. However, due to the limited number of existing reports and the lack of data from controlled clinical trials, it was impossible to prove the interaction did not exist.

Current literature and practice guidelines support the concomitant use of stimulants and alpha agonist agents to treat attention deficit hyperactivity disorder (ADHD), and there is no clear evidence of death associated with the combination.[2] There is some belief that clonidine has synergistic effects when used with stimulants in reducing behavioral symptoms of ADHD, which ultimately can result in a reduction in the stimulant dose when these medications are used concomitantly.[3]

1.2 REGULATORY HISTORY

The methylphenidate-clonidine drug interaction statement was added to the various methylphenidate and dexmethylphenidate product labels at different times (see Table 1 below for a summary of the additions).

Table 1. Timeline for the labeling addition of the methylphenidate-clonidine drug interaction statement

Date of the addition	Product name	Reason for addition
August 1, 2000	Concerta (methylphenidate)	Drug approval
April 3, 2001	Metadate CD (methylphenidate)	Drug approval
November 13, 2001	Focalin (dexmethylphenidate)	Drug approval
January 11, 2002	Ritalin IR and Ritalin SR (methylphenidate)	Changes Being Effected supplement submitted by Novartis
June 5, 2002	Ritalin LA (methylphenidate)	Drug approval
May 26, 2005	Focalin XR (dexmethylphenidate)	Drug approval
April 6, 2006	Daytrana (methylphenidate)	Drug approval

1.3 RELEVANT PREVIOUS DPV REVIEWS

- May 17, 1995[4]- The purpose of this review was to identify cases of drug interactions between clonidine and methylphenidate in children in response to a report of sudden

death in an 8-year old female treated with both products. Five serious reports were retrieved where clonidine and methylphenidate were used concomitantly. Two of these cases reported death with the first reporting an underlying cardiac issue and the second reporting a sudden death. There was limited information in the cases identified to draw any conclusions as to a potential drug interaction between clonidine and methylphenidate.

- June 11, 1997[5]. The purpose of this consult was to identify cases of deaths in children on clonidine therapy. Three additional cases of death in association with concomitant clonidine and methylphenidate use were identified. The author stated that these three cases were potentially not attributable to drug administration based on other factors described in the cases. Once again, the author concluded that the data did not provide substantial evidence of an interaction between clonidine and methylphenidate.
- August 22, 2000[6]- The purpose of this consult was to identify cases of serious cardiovascular events and sudden death when used concomitantly with psychostimulants (methylphenidate, pemoline, amphetamine, dextroamphetamine, or methamphetamine). Since the previous review in 1997, no new cases of sudden death or serious cardiovascular events were identified in patients on concomitant clonidine-psychostimulant therapy. No conclusions were made regarding the potential for a drug interaction between clonidine and the psychostimulants.

1.4 PRODUCT LABELING

The current methylphenidate and dexmethylphenidate product labels contain the following language regarding a possible drug interaction with clonidine:[7,8]

> **Drug Interactions**
>
> *Serious adverse events have been reported in concomitant use with clonidine, although no causality for the combination has been established. The safety of using methylphenidate in combination with clonidine or other centrally acting alpha-2-agonists has not been systematically evaluated.*

Due to a lack of support for an association with the combined use of clonidine and methylphenidate and serious adverse events, including death, the Catapres (clonidine hydrochloride) label, approved on April 7, 2010, no longer contains the following language[9,10]:

> **Drug Interactions**
>
> *Serious adverse events, including death, have been reported in concomitant use with methylphenidate, although no causality for the combination has been established. The safety of using clonidine in combination with methylphenidate has not been systematically evaluated.*

The product labels for dextroamphetamine, guanfacine, lisdexamfetamine, and the mixed amphetamine salts do not have this drug interaction statement.

2 METHODS AND MATERIALS

2.1 CASE DEFINITION

We only included cases of death in association with the concomitant use of a stimulant and an alpha agonist that did not report a co-existing medical disorder known or suspected to be

associated with death or a death with a known cause unrelated to an underlying medical condition (e.g. accidental deaths, homicides, motor vehicle accident, natural disease progression, overdoses, or suicides).

2.2 AERS SELECTION OF CASES

DPV searched the AERS database on April 6, 2010 for all reports with an outcome of **death** utilizing the drug interaction tool for the following drug combinations:

- Clonidine and dexmethylphenidate (n=0)
- Clonidine and methylphenidate (n=32)
- Clonidine and mixed amphetamine salts (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate) + dextroamphetamine sulfate + lisdexamfetamine (n=10)

AND

- Guanfacine and dexmethylphenidate (n=0)
- Guanfacine and methylphenidate (n=5)
- Guanfacine and mixed amphetamine salts (amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate) + dextroamphetamine sulfate + lisdexamfetamine (n=1)

**All associated trade names and active ingredients were included in our searches.

The AERS search retrieved 48 reports for all six searches combined. Of these reports, 47 were not included for further discussion for the following reasons:

- Duplicate reports (19)
- The case reported a co-existing medical condition/disorder known or suspected to be associated with death {e.g., multi-organ failure, life-threatening infection, natural disease progression} (11)
- The case reported a death with a known cause unrelated to an underlying medical condition{e.g. accidental deaths, motor vehicle accident, overdoses, or suicides} (10)
- Mistake in reporting- the patient was not taking clonidine (1)
- Case mistakenly captured in the search- the patient was on clonidine alone (1)

Additionally, there were five cases captured in our search reporting death in association with the clonidine-methylphenidate combination that were previously described in other DPV reviews and/or the literature; therefore, they were not included for discussion in this review. Of note, only one of these cases met the case definition for inclusion in this review (ISR# 4960351). Appendix B contains narrative summaries of these five cases.

The remaining one unique case met the inclusion criteria based on the case definition, and was therefore, included for further review and discussion.

2.3 CLINICAL TRIAL DATA

2.3.1 Clonidine and Psychostimulants

DPP reviewed the adverse event data submitted as part of pending NDA 22331 from the controlled trials looking at the combination of clonidine and psychostimulants. This application is seeking the indications of monotherapy and adjunctive therapy (to stimulants) for a slightly modified release formulation of clonidine hydrochloride in children and adolescents with ADHD.

2.3.2 Guanfacine and Psychostimulants

DPP reviewed the adverse event data submitted as part of pending NDA supplement 22037 S-2 from the controlled trials looking at the combination of guanfacine and psychostimulants. This supplement is seeking the indication of adjunctive therapy (to stimulants) for a long-acting formulation of guanfacine.

2.4 LITERATURE SEARCH

DPV performed a PubMed search in an attempt to identify additional case reports of death in association with the concomitant use of alpha agonists (clonidine or guanfacine) and stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts).

3 RESULTS

3.1 ADVERSE EVENTS CASES

Below is the narrative summary of the one case of death associated with the concomitant use of methylphenidate and clonidine, which met the case definition described in section 2.1.

ISR #6391595; US, 2009- A 15-year old female "suddenly fell to the ground while running" and died from "unknown causes" during treatment with both methylphenidate and clonidine (doses and durations unknown). An autopsy performed at 11.6 hours after her death reported a normal heart weight of 250 g, and the toxicology screen reported the presence of methylphenidate hydrochloride (ritalinic acid) in the blood at 240 ng/ml (normal range unknown). No further case details were provided. This case was also reported in the literature.[11]

3.2 CLINICAL TRIAL DATA

Clinical trial data are unlikely to have a sufficient number of serious and rare adverse events to have any meaningful impact on this issue, but the clinical trial data available for review were nevertheless examined for safety signals of serious adverse events.

3.2.1 Clonidine and Psychostimulants

In an adjunctive treatment study, 154 patients received clonidine along with a psychostimulant (methylphenidate or amphetamine). There were no deaths in this study. There were three serious adverse events, but none of these are considered related to study drugs, and they were not life-threatening. In general, most common adverse events were consistent with the known properties of alpha$_2$-adrenergic agonists: somnolence/fatigue.

3.2.2 Guanfacine and Psychostimulants

In the adjunctive treatment study, 302 patients received guanfacine along with a psychostimulant (methylphenidate or amphetamine). There were no deaths in this study. There were three serious adverse events, two were unrelated to study drugs, and the third was syncope in a 9-year-old, which may be related to the pharmacodynamic effects of guanfacine. This third patient was judged by the investigators to have syncope unrelated to guanfacine and completed the study without changing his dose and with no more syncopal events.

3.3 LITERATURE SEARCH

The search of PubMed did not identify any additional case reports of death in association with the concomitant use of alpha agonists (clonidine or guanfacine) and stimulants (methylphenidate, dexmethylphenidate, dextroamphetamine, lisdexamfetamine, and mixed amphetamine salts).

4 DISCUSSION

4.1 ADVERSE EVENT CASES

There are very few cases of death in people receiving the combination of a stimulant and alpha agonist in both the AERS database and the literature. Only one new case of death was identified in the AERS database associated with the concomitant use of methylphenidate and clonidine[‡]. This case provided very limited details and the cause of death was listed as unknown. While it is of course true that the absence of reporting does not necessarily mean the absence of a signal and that AERS data is subject to under-reporting, the fact remains that there is but one new case since 1997. FDA does not receive all adverse event reports that may potentially occur with a product. Many factors can influence the reporting of an event, including the length of time a product has been marketed, and publicity surrounding an event. Having said this, in 1995, there was a significant amount of publicity surrounding this issue in the news and literature, and yet FDA did not experience stimulated reporting.

To date, there has been no clear elaboration of a mechanism for the potential drug interaction when methylphenidate and clonidine are used together. There is one hypothesis described in the literature, which focuses primarily on the timing of administration of both agents: methylphenidate early in the day to treat ADHD, and clonidine at night to minimize stimulant use and to promote sleep. When clonidine is administered in the evening and methylphenidate is administered in the morning, the potential exists for a patient to experience a rebound increase in blood pressure from trough concentrations of clonidine in the morning added to the potential increase in blood pressure from morning stimulant dosing; this combined effect may ultimately result in an elevated blood pressure. [2] An elevated blood pressure, however, would not by itself lead to serious adverse events in most cases, and the cardiovascular adverse events typically associated with clonidine therapy have been seen primarily in patients with pre-existing myocardial impairments and/or who are concomitantly using sympatholytic agents.[12]

In clinical practice, the use of concomitant methylphenidate and clonidine for the management of ADHD in children and adolescents has been increasingly popular since 1992.[2] Based on a concurrency analysis performed as part of this review; there is a substantial amount of concurrent dispensing of clonidine or guanfacine with psychostimulants to pediatric patients. The proportion of patients who received a clonidine or guanfacine prescription dispensed

[‡] There was another case previously identified and described in 1994, which meets our current case definition, and is summarized in Appendix B- ISR#4960351.

concurrently with a stimulant product in the study group was approximately 12-13% and 34-36%, respectively, during the study period (utilization trends are further described in the concurrency analysis) [13] Despite the fact that the concomitant use of these drugs has increased over the years, and that there has been increasing acceptance of combination therapy to treat ADHD in the medical community, there is still an absence of reports that would support an association for a potential serious drug interaction.

Considering all of these factors, at this time there does not appear to be a drug interaction signal associated with the concomitant use of a stimulant and alpha agonist.

4.2 CLINICAL TRIAL DATA

Overall, the review of the controlled trial adverse event data did not identify any new potential safety concerns associated with the concomitant use of clonidine or guanfacine with psychostimulants. There were relatively few serious adverse events and none that were obviously drug-related.

5 CONCLUSION

There is a lack of the evidence in the available AERS data and in the controlled clinical trial data to support an association for a potential drug interaction between stimulants and alpha agonists.

6 RECOMMENDATIONS

Based on the data reviewed, in the absence of published or other data that points to risk for adverse events, we recommend updating the current methylphenidate and dexmethylphenidate labels to remove the drug interaction statement regarding methylphenidate and clonidine.

7 REFERENCES

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8 APPENDICES

8.1 APPENDIX A- APPLICATION NUMBERS AND SPONSORS

DRUG (Active Ingredient)	APPLICATION NUMBER	SPONSOR
Clonidine	17407, 18891, 22499, 22500, 76157, 70317, 70923, 70924, 70925, 70963, 70974, 70975, 70976, 71783, 71784, 71785, 77901, 78099, 78895, 91104, 20615, 22331	Boehringer Ingelheim, Tris, Aveva, Mylan, Mutual, Watson, Actavis, Dava, Vintage, Impax, Unichem, Pharmaforce, Bioniche, Shionogi
Dexmethylphenidate	21278, 21802, 77107	Novartis, Teva
Dextroamphetamine sulfate	17078, 40361, 40365, 40367, 40436, 40776, 76137, 76353	SmithKline Beecham, Barr, KV, Mallinckrodt, Outlook, Barr
Guanfacine	22037, 19032, 74145, 74673, 74796, 75109	Shire, Promius, Watson, Mikah, Mylan, Amneal
Lisdexamfetamine	21977	Shire
Methylphenidate	21121, 21514, 21259, 40306, 89601, 21419, 21475, 75629, 10187, 21284, 18029, 40220, 40300, 40321, 40410, 75450, 85799, 86428, 86429	Johnson & Johnson, Shire, UCB, Mallinckrodt, Novartis, Watson, Actavis Elizabeth,
Mixed amphetamine salts (Amphetamine aspartate, amphetamine sulfate, dextroamphetamine saccharate, dextroamphetamine sulfate)	11522, 21303, 40422, 40439, 40440, 40444, 40472	Duramed, Shire, Barr, Sandoz, Mallinckrodt, Corepharma, Teva

8.2 APPENDIX B- NARRATIVE SUMMARIES OF THE FIVE PREVIOUSLY DESCRIBED DEATH CASES

ISR# 4960351, Foreign, 2006- A 8-year old female experienced sudden death after using methylphenidate 25 mg daily for almost three years and clonidine 225 mcg daily for four months, both for unknown indications. At both four weeks and one week prior to her death, she received general anesthetics for unknown reasons resulting in two episodes of vomiting, from which she recovered. The autopsy reported the results as normal. (This case was originally reported to the AERS database in 1994 ISR# 1502861 and also described in the literature).

ISR# 1557196, US, 1995- A 7-year old male with a history of premature birth (~34 weeks gestation), cardiac abnormalities, and ADHD died while using both methylphenidate and clonidine (doses and durations unknown). He complained of "feeling ill" while at school and was pronounced dead within two hours of his initial complaint. The autopsy revealed "an enlarged, dilated heart showing no evidence of congenital malformation but with considerable fibrosis of the mitral papillary muscles and patchy fibrosis of other areas of the myocardium." The medical examiner stated that the patient's "cardiac abnormalities were sufficient to cause death regardless of the presence or absence of any therapeutic drug regimen."

ISR# 1842653, US, 1996- A 4-year old female with a history of ADHD treated with methylphenidate 25 mg daily and clonidine (dose unknown) was found to have died in her sleep after complaining of a stomachache before bed. The autopsy revealed supra-therapeutic levels of clonidine (12 ng/ml) with no other significant findings. The manner of death was ruled as accidental with the most likely mechanism of toxicity being "a cardiac conduction system dysfunction and a lethal cardiac dysrhythmia."

ISR# 3240724, US, 1999- A 10-year old male with a history of unexplained exercise-related syncope was on methylphenidate 20 mg daily for four years and transdermal clonidine 0.2 mg for approximately two months. He became dizzy after playing in a pool and collapsed. CPR was unsuccessful. An autopsy report noted normal blood levels of clonidine and the most likely cause of death to be "a congenital cardiac malformation capable of causing transient ischemia and arrhythmia."

ISR# 1651122, US, 1995- A 9-year old male treated with clonidine, methylphenidate and fluoxetine (doses, durations unknown) complained of "flu-like symptoms", experienced three grand mal seizures, and died. The coroner's report revealed elevated levels of fluoxetine and its metabolite, norfluoxetine on the order of 2-3 times greater than what is seen during routine treatment. Genetic testing was performed, which revealed a genetic defect at the cytochrome P450 CYP2D locus causing impaired fluoxetine metabolism.

Application Type/Number	Submission Type/Number	Submitter Name	Product Name
NDA-17407	ORIG-1	BOEHRINGER INGELHEIM	CATAPRES
NDA-18891	ORIG-1	BOEHRINGER INGELHEIM	CATAPRES TTS
NDA-22499	ORIG-1	TRIS PHARMA INC	CLONIDINE POLISTIREX ER ORAL SUSPENSION
NDA-22500	ORIG-1	TRIS PHARMA INC	CLONIDINE POLISTIREX ER ORAL TABLETS
ANDA-76157	ORIG-1	AVEVA DRUG DELIVERY SYSTEMS INC	CLONIDINE
ANDA-70317	ORIG-1	MYLAN PHARMACEUTICALS INC	CLONIDINE HYDROCHLORIDE
ANDA-70923	ORIG-1	MUTUAL PHARMACEUTICAL CO INC	CLONIDINE HYDROCHLORIDE
ANDA-70924	ORIG-1	MUTUAL PHARMACEUTICAL CO INC	CLONIDINE HYDROCHLORIDE
ANDA-70925	ORIG-1	MUTUAL PHARMACEUTICAL CO INC	CLONIDINE HYDROCHLORIDE
ANDA-70963	ORIG-1	WATSON LABORATORIES INC	CLONIDINE HYDROCHLORIDE
ANDA-70974	ORIG-1	ACTAVIS ELIZABETH LLC	CLONIDINE HYDROCHLORIDE
ANDA-70975	ORIG-1	ACTAVIS ELIZABETH LLC	CLONIDINE HYDROCHLORIDE
ANDA-70976	ORIG-1	ACTAVIS ELIZABETH LLC	CLONIDINE HYDROCHLORIDE
ANDA-71783	ORIG-1	DAVA PHARMACEUTICALS INC	CLONIDINE HYDROCHLORIDE
ANDA-71784	ORIG-1	DAVA PHARMACEUTICALS INC	CLONIDINE HYDROCHLORIDE
ANDA-71785	ORIG-1	DAVA PHARMACEUTICALS INC	CLONIDINE HYDROCHLORIDE
ANDA-77901	ORIG-1	VINTAGE PHARMACEUTICALS LLC	CLONIDINE HYDROCHLORIDE
ANDA-78099	ORIG-1	IMPAX LABORATORIES INC	CLONIDINE HYDROCHLORIDE
ANDA-78895	ORIG-1	UNICHEM LABORATORIES LTD	CLONIDINE HYDROCHLORIDE

ANDA-91104	ORIG-1	PHARMAFORCE INC	CLONIDINE HYDROCHLORIDE
NDA-20615	ORIG-1	BIONICHE PHARMA USA LLC	DURACLON
NDA-21278	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	FOCALIN Tablets
NDA-21802	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Focalin XR Extended-Release capsules
ANDA-77107	ORIG-1	TEVA PHARMACEUTICALS USA	DEXMETHYLPHENIDATE HYDROCHLORIDE
NDA-17078	ORIG-1	SMITHKLINE BEECHAM CORP DBA GLAXOSMITHKLINE	DEXEDRINE Spansule Capsules
ANDA-40361	ORIG-1	BARR LABORATORIES INC	DEXTROAMPHETAMINE SULFATE
ANDA-40365	ORIG-1	KV PHARMACEUTICAL CO	DEXTROAMPHETAMINE SULFATE
ANDA-40367	ORIG-1	KV PHARMACEUTICAL CO	DEXTROAMPHETAMINE SULFATE
ANDA-40436	ORIG-1	MALLINCKRODT INC	DEXTROAMPHETAMINE SULFATE
ANDA-40776	ORIG-1	OUTLOOK PHARMACEUTICALS INC	DEXTROAMPHETAMINE SULFATE
ANDA-76137	ORIG-1	BARR LABORATORIES INC	DEXTROAMPHETAMINE SULFATE
ANDA-76353	ORIG-1	MALLINCKRODT INC	DEXTROAMPHETAMINE SULFATE
NDA-22037	ORIG-1	SHIRE DEVELOPMENT INC	INTUNIV: Guanfacine SR; tablet form
NDA-19032	ORIG-1	PROMIUS PHARMA LLC	TENEX
ANDA-74145	ORIG-1	WATSON LABORATORIES INC	GUANFACINE HYDROCHLORIDE
ANDA-74673	ORIG-1	MIKAH PHARMA LLC	GUANFACINE HYDROCHLORIDE
ANDA-74796	ORIG-1	MYLAN PHARMACEUTICALS INC	GUANFACINE HYDROCHLORIDE
NDA-21977	ORIG-1	SHIRE DEVELOPMENT INC	VYVANSE (LISDEXAMFETAMINE DIMESYLATE)

NDA-21121	ORIG-1	ORTHO MCNEIL JANSSEN PHARMACEUTICAL INC	CONCERTA Extended-Release Tablets
NDA-21514	ORIG-1	SHIRE DEVELOPMENT INC	Daytrana System
NDA-21259	ORIG-1	UCB INC	Metadate CD Extended-Release capsules
ANDA-40306	ORIG-1	UCB INC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-89601	ORIG-1	UCB INC	METHYLPHENIDATE HYDROCHLORIDE
NDA-21419	ORIG-1	MALLINCKRODT INC	Methylin Solution Oral Solution
NDA-21475	ORIG-1	MALLINCKRODT INC	METHYLIN CHEWABLE TABLETS.
ANDA-75629	ORIG-1	MALLINCKRODT INC	METHYLPHENIDATE HYDROCHLORIDE
NDA-10187	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Ritalin Tablets
NDA-21284	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Ritalin LA) Extended-Release Capsules
NDA-18029	ORIG-1	NOVARTIS PHARMACEUTICALS CORP	Ritalin SR) Sustained-Release Tablets
ANDA-40220	ORIG-1	WATSON LABORATORIES INC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-40300	ORIG-1	MALLINCKRODT INC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-40321	ORIG-1	ACTAVIS ELIZABETH LLC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-40410	ORIG-1	WATSON LABORATORIES INC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-75450	ORIG-1	ACTAVIS ELIZABETH LLC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-85799	ORIG-1	UCB INC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-86428	ORIG-1	UCB INC	METHYLPHENIDATE HYDROCHLORIDE
ANDA-86429	ORIG-1	UCB INC	METHYLPHENIDATE HYDROCHLORIDE
NDA-11522	ORIG-1	TEVA WOMENS HEALTH INC	Adderall amphetamine product) tablets
NDA-21303	ORIG-1	SHIRE DEVELOPMENT INC	ADDERALL XR CAPSULES amphetamine product) Extended-Release

ANDA-40422	ORIG-1	BARR LABORATORIES INC	AMPHETAMINE ASPAR;AMPHETAMINE SULF;DEXTROAMPHETAMINE SACC;DEXTROAMPHETAMINE SULF
ANDA-40439	ORIG-1	SANDOZ INC	AMPHETAMINE ASPAR;AMPHETAMINE SULF;DEXTROAMPHETAMINE SACC;DEXTROAMPHETAMINE SULF
ANDA-40440	ORIG-1	MALLINCKRODT INC	AMPHETAMINE ASPAR;AMPHETAMINE SULF;DEXTROAMPHETAMINE SACC;DEXTROAMPHETAMINE SULF
ANDA-40444	ORIG-1	COREPHARMA LLC	AMPHETAMINE ASPAR;AMPHETAMINE SULF;DEXTROAMPHETAMINE SACC;DEXTROAMPHETAMINE SULF
ANDA-40472	ORIG-1	TEVA PHARMACEUTICALS USA	AMPHETAMINE ASPAR;AMPHETAMINE SULF;DEXTROAMPHETAMINE SACC;DEXTROAMPHETAMINE SULF
NDA-22331	SUPPL-1	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE
NDA-22331	SUPPL-2	SHIONOGI PHARMA INC	CLONIDINE HYDROCHLORIDE

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/s/

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07/06/2010

MITCHELL V Mathis
07/06/2010

MARK I AVIGAN
07/08/2010